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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GROSS, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1639	
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07/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,347	BURCH ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. GROSS	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,47,48 and 53-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,47,48 and 53-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/08;3/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Responsive to communications entered 4/7/2009. Claims 38,47-48,53-64 are pending. Claims 38,47-48,53-64 are under consideration.

Elections/Restrictions

Applicant's election without traverse of: alkylcellulose for the species of sustained release carrier and cancer pain for the species of pain in the reply filed on 3/14/2008 is again acknowledged.

Applicant clarified the statement made in the remarks filed 12/3/2008 that "the elected invention encompasses claims 38, 37,48 and 53-64" meant to include the elected species mentioned above, which is now reflected in section II of applicant's complete response entered 4/7/2009.

Priority

The present application was filed 1/25/2002 and is a CON of application 09/154,354 filed 09/17/1998 (now PAT 6,552,031) which claims benefit of provisional application 60/059,195 filed 09/17/1997.

Withdrawn Objection(s) and/or Rejection(s)

The rejection of claims 54 and 57 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain associated with COX-1/2 receptors and/or opioid receptors, does not reasonably provide enablement for every type of pain associated with the laundry list of possibilities cited in claim 54 caused by any underlying receptor/agent is hereby withdrawn in view of applicant's persuasive arguments.

Maintained Claim Rejection(s) - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 47, 48, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U.S. Patent No. 4,569,937) (Date of Patent is **Feb 11, 1986**) (of record) in view of Furst (Furst, D. E. "Meloxicam: Selective COX-2 inhibition in clinical practice" *Seminars in Arthritis and Rheumatism*, **June 1997**, *26(1)*, 21-27) (of record) and in further view of Oshlack I et al. US Pat. No. 5,472,712 (**December, 1995**) (of record) and/or Oshlack II et al. US Pat. No. 6,294,195 (9/01: effectively filed **October, 1993** or earlier) (of record) and Iyengar et al. (WO 97/25988) (Date of Patent is **July 24, 1997**) (of record).

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Please note that the above rejection has been modified from the original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

The evidence provided by the Meloxicam entry of the on-line Free Encyclopedia Wikipedia has been eliminated.

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For ***claim 38***, Baker et al. (see entire document) teach a method of effectively treating pain in humans comprising orally administering to a human patient an oral dosage form comprising two analgesic compounds and or pharmaceutically acceptable salts thereof (e.g., see abstract, "Pharmaceutical compositions of narcotic analgesics [i.e., compound #1] and ibuprofen [i.e., compound #2] have been found to exhibit unexpectedly enhanced analgesic activity [i.e., pain relief] … This synergism enables the use of lower doses of either or both drugs [i.e., two analgesic compounds] with a concomitant reduction in risk of possible side effects"; see also column 3, paragraph 1 wherein administration to a "human" is disclosed; see also column 2, lines 44-48 wherein an "oral" dosage is disclosed, "Oxycodone … are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred"; see also Examples, especially Example 1 wherein use pharmaceutical dosage forms containing "only" oxycodone and ibuprofen are set forth; see also columns 3-8 wherein "single dosage form" is disclosed; see also columns 8 and 9 wherein sequential administration is disclosed; see also columns 3 and 4 showing "sustained release" formulations). In addition, Baker et al. disclose the use of oxycodone and/or at least one pharmaceutically acceptable salt in the composition (e.g., see column 2, lines 44-48 wherein an "oral" dosage is disclosed, "Oxycodone … are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred"; see also columns 1, 2, 8-10; see also Examples, especially Example 1 wherein the use of pharmaceutical dosage forms containing "only" oxycodone and ibuprofen are set forth). In addition, Baker et al. teach the use of oxycodone and/or at least one pharmaceutically acceptable salt thereof in an amount from 2.5 mg to 800 mg in an oral dosage form (e.g., see Example 1 wherein 5 mg is disclosed; see also Examples 2-24; see also column 2; see also column 3, dosage forms section). Baker et al. also disclose the use of an NSAID like meloxicam in an amount from bout 0.5 mg to about 1500 mg for the oral dosage form (e.g., see Example 1 wherein 60 mg of Ibuprofen NSAID is disclosed; see also Examples 2-24; see also columns 2 and 3).

For ***claim 47***, Baker et al. disclose a ratio of oxycodone and/or at least one pharmaceutically acceptable salt thereof to NSAID and/or at least one pharmaceutically acceptable salt thereof is from about 0 0001:1 to about 1:1 (e.g., see column 2, lines 14-19, "(a) a narcotic analgesic [i.e., oxycodone], or a pharmaceutically acceptable salt thereof, and (b) ibuprofen [i.e., substituted by Meloxicam, see below], or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:1 to about 1:800. Preferred ratios of (a):(b) are from about 1:3 to about 1:400, and most preferred ratios are from about 1:30 to about 1:400"; see also claim 1).

For ***claim 48***, Baker et al. teach oxycodone is present in the pharmaceutically acceptable salt form (e.g., see claim 1, "A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or pharmaceutically acceptable salt thereof").

The prior art teachings of Baker et al. differ from the claimed invention as follows:

For ***claim 38, 47, 48***, Baker et al. fail to disclose compositions with Meloxicam. Baker et al. only teach the use of other NSAIDs like ibuprofen (e.g., see Baker et al., abstract). In addition, Baker et al. fail to teach the use of "a sustained release carrier in

an amount such that said oral dosage form provides a therapeutic effect for about 12 hours or longer."

For ***claim 53***, Baker et al. fail to specify the types of sustained release carriers that can be used only noted that sustained release carriers can be used in general (e.g., see Baker, column 3, second to last full paragraph).

For ***claim 54***, Baker et al. fail to teach the Markush of listed pains like Cancer pain. Baker et al. only talks about alleviating pain in general (e.g., see claim 4 drawn to a method of alleviating pain).

However, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the following limitations that are deficient in Baker et al.:

For ***claim 38, 47, 48***, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the use of Meloxicam to alleviate pain in human patients (e.g., see Furst, figure 1; see also page 23, column 2, paragraph 1 "Nabumetone was significantly … more effective than placebo and had comparable efficacy to naproxen or aspirin in the physicians' and patients' assessment of degree of pain … [further studies] showed meloxicam [7.5 mg] to have efficacy approximately equal to that of nabumetone 1,000 mg"). Thus, Meloxicam is even more effective than other NSAIDs like Nabumetone at reducing pain and can be used in smaller dosages (i.e., 7.5 mg compare to 1,000 mg). Furthermore, Meloxicam exhibits less serious gastric and renal side effects than ibuprofen because it selectively inhibits COX-2 rather than COX-1 (e.g., see Furst, abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may … [exhibit] improved tolerability"; see also page 22, column 1, last paragraph, "Meloxicam exhibited greater COX-2 selectivity than … ibuprofen … [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance … With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) … diclofenac caused significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2"; see also table 1 showing meloxicam has a better COX-2/COX-1 profiile than ibuprofen). Furst also disclose, for example, 7.5 and 15 mg doses for Meloxicam (e.g., see Table 2), which meets the from about 0.5 mg to about 1500 mg limitation for the amounts of drug present in the oral dosage form.

In addition, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the use of sustained release dosage forms for opioid analgesics, including oxycodone, which utilize sustained release carriers such as beads coated with the opioid drug or substrate layers enclosing the opioid drug for the purpose of effectuating this sustained release (e.g., see Oshlack I, abstract, "A stabilized solid controlled release formulation …"; see also column 14, paragraph 2, "A wide variety of therapeutically active agents can be used in conjunction with the present invention … [including] oxycodone"; see also column 13, line 34; see also claim 6; see also claim 50; see also claim 62; see also claim 86; see also claim 108; see also Oshlack II, abstract, see also claims; see also examples; see also column 6, line 48; see also claim 5).

The combined references of Furst, Oshlack I/II et al. and Iyengar et al. also teach the use of sustained release for Meloxicam (e.g., see Iyengar et al., paragraph bridging pages 46 and 47, "The present invention encompasses … Meloxicam"; see also page 47, first full paragraph, "The advantages of any synergistic combination therapy are obvious … Sustained release formulations are now more feasible due to the lower amounts of active ingredient necessary"; see also paragraph bridging pages 48 and 49, "The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art"). In addition, the combined references of Oshlack I/II et al. and Iyengar et al. also teach a therapeutic effect for about 12 hours or longer (e.g., see Oshclack II, abstract, "provide effective blood levels of the opioid analgesic for at least about 24 hours").

For ***claim 53***, the combined references of Furst, Oshlack I/II et al. and Iyengar et al. teach the use of sustained release carriers such as Applicants' elected alkylcellulose (e.g., see Oshlack I, title; see also column 2, second full paragraph, "It considered very desirable in the art, however, to provide a controlled release coating derived from aqueous dispersions of a hydrophobic material, such as ethyl cellulose [i.e., and alkylcellulose]"; see also column 1, lines 56-58, "Hydrophobic polymers such as certain cellulose derivatives, zein, acrylic resins, waxes, higher aliphatic alcohols, and polylactic & polyglycolic acids have been used in the prior art to develop controlled release dosage forms.").

For ***claim 54***, the combined references of Furst, Oshlack I/II and Iyengar et al. teach application of analgesics to treat, for example, Applicants' elected cancer pain (e.g., see Iyengar et al., page 47, second to last paragraph, "Such pains include chronic pain, such as neuropathic pain, and post-operative pain, pain associated with arthritis, cancer-associated pain, chronic lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, neuropathic pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis."; see also Oshlack II, column 1, line 54).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute Meloxicam as taught by the combined references of Furst, Oshlack I/II et al. and Iyengar et al. for the ibuprofen in the

ibuprofen/oxycodone compositions as taught by Baker et al. because, for example, Furst shows that meloxicam is more potent than any other NSAID at reducing pain in clinical trials (e.g., see figure 2). Furthermore, a person of skill in the art would have been motivated to use Meloxicam not only because it is more potent but also because it is safer than other NSAIDs including the ibuprofen disclosed by Baker et al. (e.g., see Furst, abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may … [exhibit] improved tolerability"; see also page 22, column 1, last paragraph, "Meloxicam exhibited greater COX-2 selectivity than … ibuprofen … [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance … With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) … diclofenac caused significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2"). Finally, a person of skill in the art would reasonably have expected to be successful because Meloxicam has been shown through extensive human clinical trials to be safe and effective especially with regard to the gastrointestinal tract (see Furst citations above), which is a preferred route of administration disclosed by Baker et al. (e.g., see Baker et al., column 4, line 13). In addition, Baker et al. explicitly state in the Background section that NSAIDs have been used to treat pain (e.g., see Baker et al., column 1, paragraph 3, "This patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone"), which would include Meloxicam (e.g., see abstract, "Nonsteroidal antiinflammatory drugs (NSAIDs) exert their actions by inhibiting cyclooxygenase (COX) … A relatively selective COX-2 inhibitor … [is] meloxicam [i.e., Meloxicam is an NSAID]"). Furthermore, Furst explicitly state that meloxicam is safer than ibuprofen (e.g., see Furst, page 22, column 1, last paragraph).

Alternatively, it is submitted that the mere substitution of one component for another to yield predictable results represents a *prima facie* case of obviousness. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). Here, it would be obvious to make a simple substitution of Meloxicam for ibuprofen because it was known at the time of filing that both provided the same antiinflammatory relief via inhibition of COX receptors (e.g., see Furst, abstract; see also Table 1). Furthermore,

this substitution would have led to predictable results based on the combined teachings noted above because again it was well known that both drugs inhibit the same COX 1/2 receptors to produce the same/similar results. Thus, a person of ordinary skill in the art would have expected antiinflammatory efficacy whether ibuprofen or meloxicam was used.

In addition, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize sustained release carriers for oxycodone including beads/layers as taught by the combined references of Furst, Oshlack I/II et al. and Iyengar et al. for use in the Baker compositions since Baker expressly states that sustained release formulations are desirable. Furthermore, a person of ordinary skill in the art would have been motivated to use these formulations to delay drug release for extended duration (e.g., see Oshclack II, abstract, ""provide effective blood levels of the opioid analgesic for at least about 24 hours"). In addition, a person of skill in the art would have been motivated to use oxycodone in a sustained release dosage because, according to Oschlack I, "The present invention provides many benefits over prior art coatings, including, but not limited to, avoidance of organic solvents which have inherent safety concerns (flammability, carcinogenicity, environmental concerns, safety in general), and extended stability which may result in extended shelf life and expiration dating" (e.g., see Oschlack I, column 5, paragraph 3). Furthermore, Oshclack II state, "provide effective blood levels of the opioid analgesic for at least about 24 hours" using controlled release (e.g., see abstract). Finally, a person of skill in the art would have reasonably expected to be successful because the combined references of Oshlack I/II et al. and Iyengar teach that these formulations can be used for opioid analgesics like Applicants' preferred oxycodone or NSAIDs like Applicants' preferred Meloxicam (e.g., see Oshlack I, claims 6, 50, 62, 86 and 108; see also Iyengar et al., paragraph bridging pages 46 and 47, "The present invention encompasses … Meloxicam"; see also page 47, first full paragraph, "The advantages of any synergistic combination therapy are obvious … Sustained release formulations are now more feasible due to the lower amounts of active ingredient necessary"; see also paragraph bridging pages 48 and 49, "The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art").

Response to Arguments

In the remarks entered 4/7/09, applicant argues there is no motivation to combine the references.

Applicant's arguments have been fully considered but they are not deemed persuasive for the following reasons.

First on p 7 third full paragraph of the response applicant argues, one of ordinary skill in art would not substitute the ibuprofen of Baker et al for the Meloxicam such as disclosed by Furst et al because the chemical structure, physical properties and pharmacokinetics of ibuprofen differ from Meloxicam. In this regard, it noted that while the examiner agrees that the two compounds are different structurally and accordingly have different pharmacology, the function of each is that of a non-steroidal antiinflammatory drug (NSAID) and notably, each of Meloxicam and ibuprofen inhibit prostaglandin synthesis by targeting the same enzyme: cyclic oxygenase 2 (COX-2). Thus, in the same manner that Tylenol may be taken instead of aspirin to alleviate a headache, each may be substituted for one another in accordance with *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385 (2007) which held simple substitution of one known element for another to obtain predictable results is obvious.

Second, from the paragraph bridging pp 7-8 through the first full paragraph on p 9 of the remarks, applicant argues the FDA could not conclude Meloxicam had fewer gastrointestinal complications than other NSAIDs as of 3/27/2000. In particular, applicant quotes a statement by Sidney Wolfe before the Food and Drug Administration's Arthritis Drugs Advisory Committee on the non-steroidal anti-inflammatory drug Celecoxib, (12/1/1998 HRG Publication #1465; IDS entry AE 12/3/2009; IFW p 1):

> [t]he Drug and Therapeutics Bulletin, the British equivalent of our Medical Letter, which is sent to all British physicians, said in its August, 1998 issue

> that "There is no convincing evidence that the risk of the severest adverse gastrointestinal events, namely peptic ulceration, perforation and bleeding, is lower with meloxicam than with other NSAIDs when given at equi-effective doses ... Meloxicam has not been compared with ibuprofen ... which comes out best in most safety assessments.
>
> Ellipsises in the original. Emphasis added.

The correspondence between the FDA and Boehringer Ingelheim (the manufacturer of Melocicam) further reflects the above, as quoted by applicant of the present claimed invention.(3/27/2000 NDA 20-298 Medical Officer Review of NDA Labeling and Safety Update; IDS entry AF 12/3/2009; IFW p 4; p 1 following letter):

> The agency [FDA] and the sponsor engaged in a series of labeling discussion centering on the nature of the meloxicam submission vis-a-vis the Cox 2 hypothesis that there may be a lower incidence of serious GI adverse events due to selective inhibition of COX2 rather than COX1 enzyme. It was the agency's position that there was insufficient pharmacology and endoscopy information to support a COX2 mechanism of action for Meloxicam. The sponsor also conducted a post hoc, combined analysis of serious GI adverse effects, but agency felt that the uncertainty in post hoc inferences could not justify their inclusion as labeling.
>
> Emphasis added.

In this vein, it is noted that the FDA's position concerned inconclusive pharmacology and endoscopy evidence regarding to Meloxicam being more selective

for COX-2 over COX-1 (found in the GI; inhibition of which causes ulcerations, etc) in humans, as opposed to Meloxicam failing to show any selectivity whatsoever, as alleged by applicant.

Assuming *arguendo* that the FDA did conclude Meloxicam is not selective for COX-2 over COX-1, it is noted the documents cited by applicant were generated *after* the current invention was made (i.e. 9/17/1997), yet in accordance with 35 USC 103, a patent may not be obtained...if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious *at the time the invention was made* to a person having ordinary skill in the art to which said subject matter pertains. As mentioned in the rejection above, It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute Meloxicam as taught by the combined references of Furst, Oshlack I/II et al. and Iyengar et al. for the ibuprofen in the ibuprofen/oxycodone compositions as taught by Baker et al. Any discouraging clinical results published in 1998 would not demotivate a person having ordinary skill in the art in 1997.

Further, solely to rebut applicant's argument, evidence provided by Churchill et al (1996 Inflammopharmacology 4:125-135) in the abstract, indicates at the time the invention was made that, unlike ibuprofen, *low concentrations* of Meloxicam exhibited specificity for hCOX-2 (human COX-2) over hCOX-1 (human COX-1) in a whole cell assay (see abstract) which the authors attribute the favourable gastrointestinal profile observed for Meloxicam compared with other NSAIDs.

Lastly, it should be noted that, in fact, low concentrations of Meloxicam were

similarly subsequently required by the FDA: the Medical Officer Review of NDA Labeling mentioned above continues "However there was a clear signal of a higher rate so serious GI adverse effects at the [high] 30 mg/day dose..," which is reflected on the drug label as a maximum daily dose of Mobic (Meloxicam) being 15 mg (3/27/2000 NDA 20-298 Final Draft Labeling; IDS entry AE 12/3/2009; IFW p 16; p 14 following letter). It should also be noted, the fact that at least additive analgesia of a selected NSAID and a selected narcotic analgesic is greater than for either alone, as disclosed by Baker et al, only serves to teach toward applicant's clamed subject matter as well as the lower doses of Meloxicam which preserves COX-2 selectivity, consistent with all the evidence mentioned above.

In conclusion, to one of ordinary skill in the art as of 9/17/1997, Meloxicam at moderate doses was shown to have selectivity for COX-2 over COX-1, providing a compound for treating pain advantageously with fewer GI side effects than ibuprofen. The subsequent 1998 clinical trials presented to the FDA, while not conclusive, were not inconsistent with this notion and according to MPEP 2143 applying a known technique (i.e. COX-2 selectivity) to a known method (additive analgesia) ready for improvement to yield predictable results is obvious.

Claims 38, 47, 48, 53-62 plus 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U.S. Patent No. 4,569,937) (Date of Patent is **Feb 11, 1986**) (of record) and Furst (Furst, D. E. "Meloxicam: Selective COX-2 inhibition in

clinical practice" *Seminars in Arthritis and Rheumatism*, **June 1997**, *26(1)*, 21-27) (of record) and Oshlack I et al. US Pat. No. 5,472,712 (**December, 1995**) (of record) and/or Oshlack II et al. US Pat. No. 6,294,195 (9/01: effectively filed **October, 1993** or earlier) (of record) and Iyengar et al. (WO 97/25988) (Date of Patent is **July 24, 1997**) (of record) in further view of Eichel et al. (U.S. Patent No. 5,376,384) (**December 27, 1994**) and Miller et al. (EP 0649657 A1) (Date of patent is **April 26, 1995**).

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Please note that the above rejection has been modified from the original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

With regard to amended new claims 63-64, Miller et al teach in European Patent application claim 3, twice-a-day dosing.

The evidence provided in the Meloxicam entry of the on-line Free Encyclopedia Wikipedia has been eliminated.

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For ***claims 38, 47, 48, 53 and 54***, the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 38, 47, 48, 53 and 54. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"); see also *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 83 (CCPA 1975); *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974).

For ***claims 55-57, 61 and 62***, the combined references of Baker et al., Furst, Oshalck I et al., Oshlack II et al., and Iyengar et al., teach all the limitations noted above in the first Baker et al. rejection (which are incorporated in their entireties herein by reference). For example, the limitations for claim 55 can be found in part in the discussion of claim 38 mentioned above. Likewise, the limitation for claim 56 can be found in the discussion of claim 53. Similarly, the limitations noted in claim 57 can be

found in the discussion of claim 54 noted above.

For ***claims 58 and 59***, the combined references also teach the method of claim 55 wherein said dosage from comprises particles, wherein said particles have diameter from about 0.1 mm to about 2.5 mm (e.g., see Oshlack I, column 9, lines 31-39, "In one preferred embodiment of the present invention, the controlled release dosage form comprises pharmaceutically acceptable beads (e.g., spheroids) [i.e., particles] containing - the active ingredient coated with a controlled release coating. The term spheroid is known in the pharmaceutical art and means, e.g., (a spherical granule having a diameter of between 0.2 and 2.5 mm especially between 0.5 and 2.0 mm").

The prior art teaching of the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. differ from the claimed invention as follows:

For ***claims 55-62***, the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. fail to teach the use of an immediate-release formed used in conjunction with a sustained release form. More specifically the combined references fail to teach an immediate release form for meloxicam and a sustained release form for oxycodone.

For ***claims 60***, the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al.fail to teach the method of claim 55 wherein the meloxicam is coated onto a table comprising oxycodone in sustained release form.

However, the combined references of Eichel et al. and Miller et al. teach the following limitations that are deficient in the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al.:

For ***claim 55-62***, the combined references of Eichel et al. and Miller et al. (see entire documents) teach the virtues of using both an immediate and sustained release dosage form (e.g., see Eichel et al., column 3, lines 10-24, "in some instances, it is desirable to mix the delayed sustained-release preparation with an immediate release drug to obtain a biphasic drug release profile … The sustained-release formulation may be part of a multi-layered table containing an immediate-release layer of acetaminophen to quickly elevate and then maintain the blood levels of acetaminophen"; see also lines 25-39; see also column 5, lines 7-11, "The multi-unit microparticles may also be admixed or concentrically coated with other fractions of an immediate-release drug to provide for both immediate and delayed sustained release of the drug"; see also lines 12-18; see also column 6, lines 37-48; see also Miller et al., paragraph bridging pages 2 and 3, ""Medicaments produced using the NSAID [i.e., meloxicam] and opioid analgesic [i.e., oxycodone] … may take a wide variety of forms … [including formulations that] give immediate release of the active ingredients upon administration or may be adapted to give delayed or sustained release or … a combination of both immediate and delayed or sustained release"). Note also that said dosage forms are effective via 12 or 24 hours (e.g., see Miller et al., claim 3). Note also the amounts for the NSAID/opioid analgesic used in the reference (e.g., see claim 8) and the disease associated pains that are being treated such as arthritis (e.g., see abstract).

For ***claims 60 and 61***, the combined references if Eichel et al. and Miller et al.

teach the use of coating the immediate release form on the surface of a table containing the sustained release form and additionally disclose, in addition to the teachings of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. noted above, wherein said sustained release carrier being (i) a sustained release coating; or (ii) incorporated into a matrix with said oxycodone (e.g.., see Eichel et al., column 3, lines 20-24, "The sustained-release formulation may be part of a multi-layered tablet containing an immediate-release layer … to quickly elevate and then maintain the blood levels [of the drug]"; see also column 4, last paragraph, The core drug may be coated on sugar spheres, blended with wax incipient, or otherwise formulated to produce core drug granules. Preferably, the core drug granules are spherical microparticles having a size range from about 500 to 15 microns"; see also column 5, paragraphs 2 and 3; see also column 6, last three paragraphs; see also claim 17, The pharmaceutical preparation of claim1 6 wherein said delayed, sustained-release component is in the form of multi-units of microparticles").

For ***claim 62***, the combined references of Eichel et al., and Miller et al. also disclose, in addition to the teachings of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. noted above, the requisite 24 hour release (e.g., see Eichel et al., column 1, lines 47 and 48, "sustained release over periods of 4 to 24 hours").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a biphasic (sustained + immediate release) drug as taught by Eichel et al. using the oxycodone + meloxicam combination as taught by the combined references of Baker et al., Furst, Oshlack I et al., Oshlack II et al., and Iyengar et al. because obtaining the best drug release profile is a goal for the administration of any drug. Furthermore, a person of ordinary skill in the art would have been motivated to use the biphasic sustained + immediate release dosage to provide both a "quick elevation" and a longer term "maintenance" of the drug in the blood (e.g., see Eichel et al., column 3, lines 10-24, "in some instances, it is desirable to mix the delayed sustained-release preparation with an immediate release drug to obtain a biphasic drug release profile … The sustained-release formulation may be part of a multi-layered table containing an immediate-release layer of acetaminophen to quickly elevate and then maintain the blood levels of acetaminophen"). Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Oshlack I, for example, teaches that oxycodone can easily be formulated into a sustained release table (e.g., see Oshlack I, abstract, "A stabilized solid controlled release formulation …"; see also column 14, paragraph 2, "A wide variety of therapeutically active agents can be used in conjunction with the present invention … [including] oxycodone"). In addition, Miller et al. state, "Medicaments produced using the NSAID [i.e., meloxicam] and opioid analgesic [i.e., oxycodone] … may take a wide variety of forms … [including formulations that] give immediate release of the active ingredients upon administration or may be adapted to give delayed or sustained release or … a combination of both immediate and delayed or sustained release" (e.g., see paragraph bridging pages 2 and 3) (emphasis added).

Response to Arguments

Applicant does not offer further arguments regarding the above obviousness rejections beyond what was set forth with regard to the 35 U.S.C. § 103 rejection, above. To the extent that Applicant is merely repeating their previous argument, the Examiner contends that those issues were adequately addressed in the above section, which are incorporated in their entireties herein by reference.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571 272 0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/ Christopher S. F. Low /
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